REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 1, 13-14, 20 and 30-31 are currently amended, and claim 5 is cancelled. Claims 1-4 and 6-31 are currently pending.

Support for the amendments to the claims can be found in the originally filed claims and throughout the specification. Claim 1 has been amended to recite the features of claim 5. Claim 14 has been amended to correct the typographical error of the period being omitted at the end of the sentence. Claims 13 and 20 have been amended to recite that the methods are *in vitro* methods. Support for these amendments can be found, for example, at page 30, line 2; page 38 line 11; and page 46, lines 29-30, which indicate that the target cells are cell lines (*i.e.*, *in vitro*). Claims 30 and 31 have been amended to recite an "isolated somatic cell," as suggested by the examiner.

Reconsideration of the pending application is respectfully requested.

Claim Rejections under 35 U.S.C. § 101

The examiner indicated that claims 30-31 were rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The examiner indicated that redrafting the claims to recite an "isolated somatic cell" would be remedial. Claims 30 and 31 have been so amended.

Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 101 be withdrawn.

Claims Rejections under 35 U.S.C. §112, first paragraph (Written Description)

Claims 1-31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The present invention provides vectors and methods for disruption of a gene of interest using a gene targeting construct. In particular, the claims recite a somatic cell gene targeting vector comprising a gene targeting construct comprising a first cloning site operably linked to a DNA encoding a positive selection marker, a second cloning site and a first polyadenylation sequence, wherein the construct is promoterless, wherein the first cloning site comprises a first DNA segment that is homologous to a first genomic target sequence and the second cloning site comprises a second DNA segment that is homologous to a second genomic target sequence; and an expression cassette comprising a promoter operably linked to DNA encoding a negative selection marker and a second polyadenylation sequence, and a method for disrupting a gene of interest in a somatic cell using this claimed vector.

Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. MPEP § 2163. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art.

In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. See, e.g., *In re Hayes Microcomputer Products, Inc. Patent Litigation*, 982 F.2d 1527, 1534-35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992) ("[A]n inventor is not required to describe every detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains."). A patent specification need not teach, and preferably omits, what is well

known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

Applicant asserts that the specification provides adequate written description for the claimed invention. The relevant art area was mature at the time the application was filed. Positive-negative selector (PNS) vectors were known at the time the application was filed (*see, e.g.*, U.S. Patent 5,631,153 (Capecchi *et al.*) and Sedivy *et al.*, *TIG* 15:88-90 (1999), both of record). One of skill in the art would be aware that PNS vectors successfully could be used in a variety of cell types (*see, e.g.,* Gallego *et al.*, *Plant Molecular Biology*, 39:83-93 (1999) (plant cells); Thykjaer *et al.*, *Plant Molecular Biology*, 35:523-530 (1997) (plant cells); Chen *et al.*, *Aquaculture*, 214:67-79 (2002) (animal cells)). Once the inventors instructed the person of skill what pieces needed to go into the construct, one of skill in the art would know the molecular biology necessary to make a construct.

The examiner cites to two review articles, one by Wang et al., *Reproductive Biology and Endocrinology* 1:103 (2003), and the other by Norgren, *Reproductive Biology and Endocrinology* 2:40 (2004), to support the proposition that a skilled artisan would not have adequate direction in the specification and the art known at the time the application was filed to make or use the claimed invention. The examiner indicates that not all genes are able to undergo homologous recombination using a selection method equally, due to length of the targeted gene, its location of the chromosome proximity to a strong promoter (*citing* Wang et al., p. 3 of 8, right column, paragraph 2). These parameters, however, were cited by Wang et al. as being difficulties with inducing homologous recombination in mouse ES cells, not in somatic cells, as recited by the present claims.

The examiner indicates that not all gene targeting events result in functional disruption of the gene of interest (*citing* Norgren, p. 5 of 8, left column, paragraph 2), and that some genes are impossible to target using promoterless targeting vectors due to the lack of active promoters for some genes in some cell types (*citing* Wang et al., p. 6 of 8, left column, conclusion paragraph). This appears to be an enablement rejection rather than a written description rejection. Applicant asserts that one of skill in the art, who had knowledge of promoterless vectors, would know that an active promoter must be present in a target gene in order for a promoterless vector to be used to knockdown the particular target gene. A claimed invention that may not possess a given use

would be excluded from the claims by the one of skill in the art. The presence of potentially inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. One must apply an undue experimentation test. The proper standard is whether a skilled person could determine which embodiments would be operative or inoperative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). The Examiner has reached her conclusion of a lack of a sufficient disclosure without applying this standard.

Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph (written description) be withdrawn.

Claims Rejections under 35 U.S.C. §112, first paragraph (Enablement)

Claims 13-31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner states that the specification, while being enabling for *in vitro* methods of disrupting a TRAF gene, does not reasonably provide enablement for *in vivo* methods of disrupting any gene of interest or *in vitro* methods of disrupting any non-TRAF gene of interest in any cell. The examiner discusses at length the lack of enablement of the present invention for gene therapy and nuclear transfer cloning. For example, on page 8, item 4, the examiner states that Applicants have provided no specific guidance on how the method might be used to disrupt gene expression in a somatic cell *in vivo* such as for gene therapy or in a somatic cell for used in nuclear transfer cloning.

Applicant respectfully submits, however, that the examiner is over-stating the scope of the pending claims. Applicant does not claim methods of gene therapy or nuclear transfer cloning. The claims simply recite methods of disrupting a gene of interest in a somatic cell *in vitro*, such as to study the function of gene (specification at page 9, line 7) or to create cell lines (specification at page 30, line 2; page 38, line 11; and page 46 lines 29-30). As discussed above, Applicant asserts that the relevant art area was mature at the time the application was filed. At the time the application was filed, one of skill in the art would be aware of positive-negative selector (PNS) vectors that could be used in a variety of cell types, and would have known the molecular biology necessary to know how to make a construct, once the inventors instructed the

person of skill what pieces needed to go into the construct. Thus, Applicant asserts that the claims are adequately enabled.

Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph (enablement) be withdrawn.

Claims Rejections under 35 U.S.C. §103(a)

Claims 1-12 are rejected under 35 U.S.C. §103(a) as being unpatenable over Capecchi et al. (U.S. Patent No. 5,631,153) in view of Sedivy et al. (Trends in Gen. 15:88-90 (1999)).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. MPEP Section 706.02(j).

Independent claim 1 recites a somatic cell gene targeting vector comprising a gene targeting construct comprising a first cloning site operably linked to a DNA encoding a positive selection marker, a second cloning site and a first polyadenylation sequence, wherein the construct is promoterless, wherein the first cloning site comprises a first DNA segment that is homologous to a first genomic target sequence and the second cloning site comprises a second DNA segment that is homologous to a second genomic target sequence; and an expression cassette comprising a promoter operably linked to DNA encoding a negative selection marker and a second polyadenylation sequence. Claims 2-12 depend from claim 1.

Capecchi et al. disclose positive-negative selector (PNS) vectors for modifying a target DNA sequence contained in the genome of a target cell capable of homologous recombination. The vectors comprise a first DNA sequence substantially homologous a first region of a target DNA sequence, a second DNA sequence substantially homologous to a second region of a target DNA sequence, a third DNA sequence positioned between the first and second DNA sequences that encodes a positive selection marker (which can be a promoterless positive selection marker),

and a fourth DNA sequence encoding a negative selection marker. Capecchi et al. list a number of regulatory sequences for use with positive and/or negative selection markers.

Capecchi et al. do not disclose polyadenylation sequences operably linked to the positive selection marker, as recited by claim 1. Further, Capecchi et al. do not disclose excision of the positive selection sequences using site-specific recombination sequences, such as loxP sequences (as recited by claims 2-4). Instead, Capecchi et al. teach that the positive selection sequences can excised by homologous recombination (col. 11, lines 3-6). They teach a detailed method where the positive selection marker is located in the intron of the targeted gene, and contains an independent functional promoter, *i.e.*, it is not promoterless (col. 11, lines 27-56). Moreover, Capecchi et al. do not specifically disclose that the promoter could be a weak promoter (as recited by claim 8), and does not specifically mention the PGK or RSV promoter (as recited by claim 9 or 10).

Sedivy does not remedy the deficiencies of Capecchi et al. Sedivy discuss PNS vectors where the positively and negatively selectable genes are functionally independent expression cassettes, and each contains its own promoter and polyadenylation signals (p. 88, second column and Fig. 1). Sedivy does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector, as recited in claim 1. Sedivy mentions theoretically the possibility of sequential targeting of second allele, but provides no technical details in this review. He cites a reference in which a cre/lox system was used in ES cells to recycle a targeting vector. In that paper, the cre/lox system is used to remove a PNS cassette (positive-negative selection cassette that includes both a promoter-driven neo resistance gene as well as a thymidine kinase gene). This might allow the PNS cassette to be used in subsequent rounds of targeting. In contrast, the present invention uses the site-specific recombination sequences to remove a promoterless neo gene (the promoterless neo gene is not considered a PNS cassette). Since Sedivy does not teach or suggest a promoterless positive selection marker, Sedivy can not teach the combination of a promoterless positive selection marker in combination with a cre/lox system.

Therefore, since neither of the cited references teach nor suggest a promoterless PNS vector containing a polyadenylation sequence, the cited references even when combined do not teach or suggest all the features of claims 1-12. Further, since neither reference teaches or

suggests the use of site-specific recombination sequences in a promoterless PNS vector, the cited references even when combined do not teach or suggest all the features of claims 2-4. Moreover, since neither reference discuss the use of a weak promoter (as recited by claim 8), and does not specifically mention the PGK or RSV promoter (as recited by claim 9 or 10), these claims are not obvious over the cited art.

Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicant respectfully requests a favorable examination of the merits of this patent application. The Examiner is invited to telephone Applicant's attorney at (952) 876-4091 to facilitate prosecution of this application. Please charge any fees deemed necessary to Deposit Account 50-3503.

Respectfully submitted,

Date: 7 February 2006

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